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Patent
Attorney's Docket No. 003300-765

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	
Kjell OLMARKER et al.	Group Art Unit: 1646
Application No.: 09/826.893	Examiner: Eileen B. O'Hara
Filed: April 6, 2001	Confirmation No.: 3406
For: USE OF CERTAIN DRUGS FOR TREATING NERVE ROOT INJURY	

DECLARATION BY JOINT INVENTORS UNDER 37 C.F.R. § 1.131

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Kjell OLMARKER and I, Björn RYDEVIK, both citizens of Sweden, hereby state as follows:

1. That I am a joint inventor of subject matter claimed in U.S. Patent Application Serial No. 09/826,893, filed April 6, 2001, which is assigned to A+ Science Invest AB of Göteborg, Sweden.

2. That I am making this declaration to show invention of the claimed subject matter from a time prior to the filing date of U.S. Patent No. 6,419,944, which is April 5, 2001.

3. That the claimed subject matter was conceived prior to April 5, 2001 and the filing of the subject Application was diligently pursued from at least a period before April 5, 2001 until the Application was filed on April 6, 2001.

4. That conception of the claimed subject matter prior to April 5, 2001 is demonstrated at least by its description in a draft patent application that was prepared prior to April 5, 2001.

5. That Exhibit A, attached, is a copy of pages 1-3 and 6 of the draft patent application, describing the claimed subject matter, that was transmitted by facsimile to patent attorneys in the United States at the firm of Burns, Doane, Swecker, and Mathis on April 3, 2001.

6. That diligence in the period from at least April 3, 2001, when the draft application was transmitted to representatives in the United States, until the subject Application was filed on April 6, 2001 is demonstrated by the brevity of this period during which corrections and revisions to

the draft application were made through communications with patent representatives in the United States via representatives in Sweden.

7. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: May 21 2003

Kjell OLMARKER

Date: May 21, 2003

Björn RYDEVIK

EXHIBIT A

USE OF CERTAIN DRUGS FOR TREATING NERVE ROOT INJURY

This application is a continuation-in-part application of the United States Patent Application entitled "Use of Certain Drugs for Treating Nerve Root Injury" field January 17, 2001 as a National Stage of International Application No. PCT/SE99/01671, filed 23 September 1999, which claims benefit of Swedish Applications 9803276-6 and 9803710-4 filed respectively 25 September 1998 and 29 October 1998.

Technical Field

The present invention relates to a method for treating nerve disorders in a mammal by administering a TNF-α inhibitor. The invention also relates to the use of a TNF-α inhibitor in the preparation of pharmaceutical compositions for the treatment of nerve root injury.

The object of the present invention is to obtain a possibility to treat nerve root injury induced by disk herniation, which may turn up as radiating pain into the arm or leg (sciatica), by blocking disk related cytokines.

Background of the invention

Disk herniation is a troublesome disorder, which can cause pronounced pain and muscle dysfunction, and thereby loss of ability to work. A herniation may occur in any disk in the spine but herniations in the lumbar and the cervical spine are most common. A disk herniation in the cervical spine may induce radiating pain and muscle dysfunction in the arm and herniation in the lumbar spine may induce radiating pain and muscle dysfunction in the leg. The radiating pain in the leg is generally referred to a "sciatica". Disk herniation will cause trouble to a varying degree, and the pain may last for one or two months or in severe cases up to 6 months. The arm or leg

pain that can occur as a result of disk herniation can be very intense and may thus affect the individual patient's whole life situation during the sickness period.

US-A-5,703,092 discloses the use of hydroxamic acid compounds and carbocyclic acids as metalloproteinase and TNF inhibitors, and in particular in treatment of arthritis and other related inflammatory diseases. No use of these compounds for the treatment of nerve root injuries is disclosed or hinted at.

US-A-4,925,833 discloses the use of tetracyclines to enhance bone protein syntheses, and treatment of osteoporosis.

US-A-4,666,897 discloses inhibition of mammalian collagenolytic enzymes by tetracyclines. The collagenolytic activity is manifested by excessive bone resorption, periodontal disease, rheumatoid arthritis, ulceration of cornea, or resorption of skin or other connective tissue collagen.

Neither of these latter two documents mentions nerve root injury or the treatment thereof.

Description of the present invention

It has now surprisingly been shown possible to be able to treat nerve root injuries, or at least alleviate the symptoms of nerve root injuries by using a pharmaceutical composition comprising an therapeutically active amount of a TNF-α inhibitor, for example selected from the group consisting of metalloproteinase inhibitors excluding methylprednisolone, tetracyclines including chemically modified tetracyclines, quinolones, corticosteroids, thalidomide, lazaroides, pentoxyphylline, hydroxamic acid derivatives, napthopyrans, soluble cytokine receptors, monoclonal antibodies towards TNF-α, amrinone, pimobendan, vesnarinone, phosphodiesterase III inhibitors, lactoferrin and lactoferrin derived analogous, and melatonin in the form of bases or addition salts together with a pharmaceutically acceptable carrier.

By "therapeutically active amount" is intend d an amount that will lead to the desired therapeutical effect, i.e. an amount that will lead to an improvement of the patient's condition.

Compounds that possess this activity are for example tetracyclines, such as tetracycline, doxycycline, lymecycline, oxytetracycline, minocycline, and chemically modified tetracyclines dedimethylaminotetracycline, hydroxamic acid compounds, carbocyclic acids and derivatives, thalidomide, lazaroides, pentoxyphylline, napthopyrans, soluble cytokine receptors, monoclonal antibodies towards TNF-α, amrinone, pimobendan, vesnarinone, phosphodiesterase III inhibitors, lactoferrin and lactoferrin derived analogous, melatonin, norfloxacine, ofloxacine, ciprofloxacine, gatifloxacine, pefloxacine, lomefloxacine, and temafloxacine. These can be present as bases or in the form of addition salts, whichever possesses the best pharmaceutical effect, and best property to be brought into a pharmaceutical suitable composition. A more complete list is given below.

As stated above, there are several different types of TNF blocking substances and pharmacological preparations that may be used according to the invention, and those substances may be grouped in different subclasses:

- Specific TNF blocking substances, such as
  - Monoclonal antibodies, e.g. infliximab, CDP-571 (HUMICADE™), D2E7, CDP-870, MAP-195F;
  - Soluble cytokine receptors; etanercept, lenercept, pegylated TNF-receptor type I, TBP-1;
  - TNF-receptor antagonists;
  - Antisense oligonucleotides; ISIS-104838;
- Non-specific TNF blocking substances, such as:
  - MMP-inhibitorer (or TACE-inhibitors, i.e. TNF Alpha Converting Enzyme-inhibitors);
    - Tetracyclines, for example Doxycycline, Lymecycline, Oxitetracycline, Tetracycline, Minocycline

The substances according to the invention may also be administered in combination with other drugs or compounds, provided that these other drugs or compounds do not eliminate the effects desired according to the present invention, i.e. the effect on TNF.

The invention further relates to a method for inhibiting the symptoms of nerve root injury.

The effects of doxycycline, soluble cytokine-receptors, and monoclonal cytokine-antibodies have been studied and the methods used and results obtained are disclosed below.

The compounds of the invention can be administered in a variety of dosage forms, e.g., orally (per os), in the form of tablets, capsules, sugar or film coated tablets, liquid solutions; rectally, in the form of suppositories; parenterally, e.g., intramuscularly (i.m.), subcutaneous (s.c.), intracerebroventricular (i.c.v.), epidurally, transepidermally or by intravenous (i.v.) injection or infusion; by inhalation; or intranasally. The therapeutic regimen for the different clinical syndromes must be adapted to the type of pathology taken in to account, as usual, also the mute of administration, the form in which the compound is administered and age, weight, and condition of the subject involved.

The oral route is employed, in general, for all conditions, requiring such compounds. In emergency cases preference is given to intravenous injection. For these purposes the compounds of the invention can be administered orally at doses ranging from about 20 to about 1500 mg/day. Of course, these dosage regimens may be adjusted to provide the optimal therapeutic response.

The nature of the pharmaceutical composition containing the compounds of the invention in association with pharmaceutically acceptable carriers or diluents will, of course, depend upon the desired route of administration. The composition may be formulated in the conventional manner with the usual ingredients. For example,